REMARKS

I. Issue concerning response to Restriction Requirement of March 31, 2009

In the Office Action issued March 31, 2009, the Examiner presented a two-way restriction of Applicants' claims, as between the following groups:

Group I: Claims 39-73, drawn to a method for treating an individual with a tumor resistant or refractory to a taxane, comprising administering to the individual an effective amount of a compound of the structure provided in claim 39; and

Group II: Claims 74-107, drawn to an article of manufacture and packaged pharmaceutical composition including a label which indicates that said pharmaceutical composition can be used for the treatment of an individual suffering from a cancer or tumor resistant or refractory to a taxane, wherein said pharmaceutical composition comprises a compound of claim 74.

Election of Group

In addition to electing Group I or II for further examination, the Examiner also required election of a particular taxane (if present), election of a specific cancer type, and election of a single anti-cancer therapeutic co-agent (if present).

In the response filed May 29, 2009, Applicants provisionally elected for examination (with traverse) the claims of Group I (i.e., Claims 39-73) drawn to a method for treating an individual with a tumor resistant or refractory to a taxane, comprising administering to the individual an effective amount of a compound of the structure provided in claim 39, for further examination on the merits.

For the required election of species, Applicants elected the method in the absence of a taxane. For a particular cancer/tumor, Applicants elected prostate cancer. And finally, for a particular anti-cancer therapeutic co-agent, Applicants elected the method in the absence of a co-agent.

Applicants stated in the response that the claims readable on the elected species were Claims 39-47, 52-55, 57-65, and 70-72.

Therefore, the subject matter that should presently be under consideration is a method for the treatment of prostate cancer comprising administration of satraplatin and wherein the cancer is resistant or refractory to a taxane and the method does not include administration of a co-agent. The claims readable on this method are as set forth above. However, in the first Office Action and the present Office Action on page 2, the Examiner has included among the claims withdrawn

from consideration (as a result of the Restriction being made final) Claims 43, 44, 53, 54, 55, 61, 62, 70, 71, and 72, which are claims included in Applicants' list of claims readable on the elected invention and that were all part of the Examiner's Group I restriction group. As such, Applicants believe the Examiner has mistakenly withdrawn from consideration claims that cover elected subject matter.

Applicants assert that Claims 43, 44, 53, 54, 55, 61, 62, 70, 71, and 72 recite subject matter that is readable on the elected invention and it is requested that these claims be rejoined and included with the claims currently under examination.

II. 35 U.S.C. §112, first paragraph

The Examiner has raised an enablement objection under 35 U.S.C. §112, first paragraph against Claims 39-42, 45-47, 52, 57-60, and 63-65. The Examiner is essentially alleging that the in vitro data demonstrating cancer treatment presented in the present specification is not predictive of whether the compounds tested therein would actually be suitable for treatment of human cancers regardless of the positive results demonstrated in the assays. According to the Examiner,

> "Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonably [sic] degree of predictability." (See, Office Action, page 3.)

Applicants respectfully assert that the issue is whether one skilled in the art, after reviewing Applicants' data presented in the specification would be convinced that the results demonstrate an effectiveness for cancer treatment in humans. The Examiner is disregarding the fact that Applicants have demonstrated a platinum-based chemotherapeutic agent is effective at killing tumor cells resistant or refractory to a taxane in widely-accepted models of cancer treatment. The Examiner has provided no support for why one skilled in the art would doubt that the data disclosed in the specification would not be an indication that the disclosed compounds would not be effective in the treatment of human cancers other than citation to several references that indicate some scientists have suspicions about extrapolating some assay data to humans.

However, the present specification is not seeking to discover whether new, previously unknown compounds may be suitable for treating cancers in humans. As disclosed in the specification, platinum-based compounds have been shown to have efficacy in the treatment of human cancers,

> "Platinum compounds are among the most active chemotherapeutic agents available for the treatment of a variety of malignancies, including testicular and ovarian carcinoma . . Satraplatin has advantages compared to cisplatin due it its oral availability and favourable safety profile, such as the absence of kidney- and neurotoxicity. Activity of satraplatin has been shown in prostate, ovarian and SCL carcinoma patients. (See, page 1, lines 19-27.)

Applicants respectfully assert that the specification provides ample guidance, direction and data from results generated in art-accepted cancer models to convince one skilled in the art that satraplatin (or satraplatin metabolites) is an effective treatment for various cancers in humans including prostate cancer that is resistant or refractory to a taxane.

For example, as set forth in the specification in Example 1 beginning on page 50, Applicants demonstrated, using the NCI-Adr resistant cell subline first described in Vickers et al., *Mol. Endocrinology*, 3(1): 157-164 (1989) that taxane-resistant tumor cells, where the resistance is mediated through P-glycoprotein, were, surprisingly, susceptible to treatment with satraplatin. (See, Table 1, "Cellular IC50's of Satraplatin and metabolites in Paclitaxel resistant cells".)

As seen in Table 1, NCI-Adr-resistant tumor cells were highly resistant to paclitaxel and taxotere (relative resistance of 46 and 33, respectively) but highly susceptible to treatment with JM216, JM118, and JM383 (relative resistance 1.1, 1.1, and 0.93 respectively).

In tumor cells where the taxane resistance is mediated through tubulin, Applicants demonstrated that cancer cells that are highly resistant to the taxanes paclitaxel and taxotere were yet highly susceptible to treatment with satraplatin (JM216) as well as the satraplatin metabolites JM118 and JM383. As described in Example 1B, beginning on page 51, tubulin mutated, paclitaxel-resistant human ovarian carcinoma cells derived from cell line 1A9-PTX10 were treated with either paclitaxel, taxotere, satraplatin (JM216), JM118, or JM383 and the results are presented in Table 1. As seen in Table 1, (page 53) the relative resistance of these tumor cells to paclitaxel and taxotere was high, 42.6 and 105.8, respectively. In sharp contrast, these cancer cells were highly susceptible to satraplatin and satraplatin derivatives: relative resistance to JM216, JM118 and JM383, was 1.3, 3.1, and 2.1, respectively.

In another tumor cell cancer model where the resistance is mediated through an ABC transporter, colon carcinoma cells (HT29/MIT), were treated with either satraplatin or JM118. As seen in Table 3 on page 56 of the specification, the HT/29/MIT carcinoma cells had a relative resistance to mitoxantrone of 175, however these cells were highly susceptible to satraplatin and JM118 (relative resistance of 1.6 and 1.3, respectively).

Similarly, the etoposide-resistant breast cancer cell line MCF-7/VP, a cell line whose resistance is also mediated through an ABC transporter, had a relative resistance to etoposide of >20, however these cells were highly susceptible to satraplatin and JM118 (relative resistance of 1.6 and 1.1, respectively).

Therefore, the specification clearly demonstrates, by presenting data in art-accepted models for cancer treatment, that cancer cells having a resistance to taxane treatment are highly susceptible to treatment with satraplatin and derivatives thereof. Moreover, much of the data presented relate to treatment of cell types wherein the mechanism of refractoriness toward taxanes is believed to be known, namely, taxane resistance is mediated by mutation of tubulin or mediated through overexpression of an ABC transporter. Therefore, the Examiner's contention that,

> "[T]he lack of guidance provided in the specification the presence of a working example which does not address the issue of the efficacy of the control and **the negative teachings in the prior art** balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written." (See, Office Action, page 6, emphasis added.),

is unfounded. As stated above, the Examiner has cited several references to support the contention that assay results presented in art-accepted models of cancer treatment can never be predictive of the effectiveness these compounds would have in the treatment of human cancer. Applicants respectfully assert that the cited references do not support this contention at all.

With respect to the reference to the T. Gura article, the Examiner has lifted a general statement from this article appearing in the News section of *Science* magazine in 1997 to support the sweeping proposition that results of cancer treatments tested using *in vitro* and *in vivo* cancer models cannot be probative of effectiveness in human patients. This is too pat a conclusion to draw from the Gura article, and it discounts all of the knowledge and understanding that must be credited to the person of ordinary skill in this art in 2005, over seven years after the Gura article was published.

First, the title of this article alone, "Systems For Identifying New Drugs Are Often Faulty," is a clear indication that it is irrelevant to evaluating the present invention, because the article clearly relates to discovery of new drugs rather than discoveries made on established drugs. Even if it is accepted, for the sake of argument, that *in vitro* and animal models cannot ever predict effectiveness of model-tested drugs in humans, the effectiveness in humans of the drugs recited in Applicants' claims has already been established, *ergo* the predictive value of the model for a new drug of unknown effectiveness is of little relevance here.

The present invention relates to a discovery on the use of platinum-based drugs which have already been shown to be well tolerated in humans and are known to be effective anti-cancer drugs in humans. Thus, the data presented in the present application shows the relative performance of these platinum-based compounds and the surprising results that they are effective at treating tumors that are resistant to taxanes where the resistance is mediated through multiple different mechanisms. (See, specification, page 4, lines 23-29.) The fact that these compounds are effective to destroy tumor cells that have developed a resistance to taxanes is meaningful to the person of ordinary skill in the art, in spite of the general reporting of Gura (more than 7 years before the invention) that animal results in drugs untested in humans are not always predictive of effectiveness in humans. The question before the Examiner is whether a person of ordinary skill in the art (who is by definition aware of the efficacy of platinum compounds to treat cancer in humans) would agree with Applicants that the results presented in the application show an unexpected and surprising effectiveness against tumor cells that have developed the above-described type of resistance to treatment.

It is pointed out that Gura is not a review of Applicants' methods or data, therefore it is not direct evidence that the actual data presented in the application would not be taken as meaningful by a person of ordinary skill in the art. Gura provides a general statement (from 1997) about the predictive value of models, not about the value of assay data presented with art-accepted cancer models such as that presented in the application. The experiments presented in the application show the performance of the method of the invention compared against relevant controls: i.e., cells that were sensitive to treatment with taxanes. The results of the claimed method are surprising in comparison to the controls. And in this context of controlled experimentation, those surprisingly results are probative of the suitability of the claimed compounds in the treatment of tumors that have developed a resistance to taxanes, regardless of the notion proposed by the Examiner that the experimental models employed might not have been predictive of successful treatment in humans.

The Examiner has cited the Gura article in order to dismiss the unexpected results presented in the present application but has given no indication why a person of ordinary skill in the art would reach the same conclusion after reading Applicants' specification. The statement made by Alan Oliff that the Examiner references from the article, i.e., "The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all", was not a conclusion reached by Trisha Gura or Alin Oliff or any skilled artisan who has had an opportunity to review Applicants' extensive data, and, as such, the Examiner is in no position to prefer a conclusion that, "the specification appears to be silent on any suggestion between the *in vitro* testing and *in vivo* success." Applicants respectfully assert that a person of ordinary skill in the field of cancer therapy, viewing the data presented in the application would conclude that the results are impressive and demonstrate a surprising, novel, and inventive method.

To further support the rejection, the Examiner cites Freshney, Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, for the proposition that,

> "It is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney . . . teach that it is recognized in the art that there are many differences between cultured cells and counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissues are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light." (See, Office Action, paragraph bridging pages 3 and 4.)

The Freshney reference, which predates Applicants' filing date by 18 years, discusses the advantages and disadvantages of tissue culture. The Examiner has given no indication how the issues discussed in Freshney relate to the culture and assay data presented with the established tumor cell lines used in the present specification, all of which were developed after the publication of this reference. There is no indication that the advantages and/or disadvantages discussed by Freshney in any way relate to the tumor cell lines used in the present specification and there is no indication that Freshney has ever attempted to culture the tumor cell lines disclosed in the present specification. Therefore, Applicants respectfully assert that the Freshney reference is in no way applicable or indicative that the assay data presented in the present

specification is in any way unreliable or that one skilled in the art would believe the tumor cells were in any way compromised during the experiments, rendering the results unreliable.

The Examiner cites G. Dermer, *Bio/Technology*, 12: 30 (1994) stating that this article,

> [T]eaches that, 'petri dish cancer' is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradiction between life on the bottom of a lab dish and in the body has been scientific characteristics different form [sic] those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions." (See, Office Action, page 4.)

This Dermer article, entitled "*Another Anniversary for the War on Cancer*" appeared in The Last Word section of this Bio/Technology publication and predates Applicants' disclosure by 11 years. Similar to the Gura article discussed above, it is not a scientific study but a personal opinion espoused by Dermer related to the use of cell lines to discover new drugs for cancer treatment. According to Dermer,

> "Why don't we have a cancer cure by now? The answer, **in my opinion**, is basic and essentially simple: The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body." (See, left column, second paragraph; emphasis added.)
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> "The widely disparate character of human tumor cell lines contributes greatly to chemotherapy's continued ineffectiveness against cancer. New drugs are selected for human trials because they kill tumor cell lines in the laboratory." (See, right column, first paragraph.)

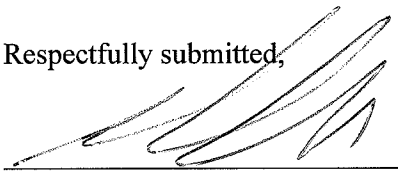
As stated above, the present invention relates to a surprising discovery on the use of platinum-based drugs which have already been shown to be well tolerated in humans and are known to be effective anti-cancer drugs in humans, the discovery being that certain platinum-based compounds are effective against tumors that are resistant to treatment with taxanes. Hence, the discussion by Dermer related to cell lines and the testing of new drugs as potential treatments for cancer in inapposite. The results in the specification are presented in art-accepted models of cancer therapy. Regardless of the fact that Gerald Dermer expresses skepticism with the cell lines

being used in 1994 to test the efficacy of new compounds for potential cancer treatment, Gerald Dermer has not reviewed Applicants' methods or data, and his generalized opinion on cell lines can not be held as direct evidence that the actual data presented in the application would not be taken as meaningful by a person of ordinary skill in the art.

In view of the foregoing remarks and the data originally presented in the application, reconsideration and allowance of Claims 39-47, 52-55, 57-65, and 70-72 are respectfully requested.

For the reasons set forth above, reconsideration and allowance of all claims readable on the elected invention, i.e., Claims 39-47, 52-55, 57-65, and 70-72 are respectfully requested.

Respectfully submitted,



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